

## Border Health Spans the Continent

IN THIS ISSUE Elena Nightingale, MD, reports findings and makes recommendations about "border" health problems.<sup>1</sup> These problems grow and spread as poverty, tensions, and violence grow and spread. The border is not simply a line but a region and perhaps a condition. Every day, political and economic refugees enter the United States from Mexico and Central America. They travel extensively. Physicians in all parts of the country need to appreciate and act on the issues Dr Nightingale presents.

A student and I recently saw a patient in a clinic at the University of California, San Francisco. The 65-year-old widow, visiting from El Salvador, had head, shoulder, and back pain. The usual history was not remarkable, and there were no positive physical findings. Through a translator, I asked about her experiences in the war. She said that several of her young relatives had disappeared and that she worried constantly about the others. She felt that army helicopter gunships were far more terrifying and unpredictable than guerrillas. She herself had associated flares in her symptoms with increased disruption caused by the war. She wondered if her pain could be related to fear. Later, when I asked about her sleep patterns, she said, "I have terrible nightmares when I am in this country." What about when she is in El Salvador? "There, I don't sleep at all."

Border health is part of physicians' practices wherever they may be. We need to be alert to subtle wounds caused by the effects of civil unrest on noncombatants. We need to work toward humane refugee and foreign aid policies that encourage good health.

LINDA HAWES CLEVER, MD

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## How We Get Stoned

IN THE HIPPOCRATIC OATH, physicians swear by various deities that "I will not cut persons laboring under the stone, but will leave this to be done by men who are practitioners of this work." Unfortunately, many still labor under the stone. The practitioners of this work, our urological colleagues, are increasingly armed with powerful new technologies for fragmenting and removing kidney stones, but these concretions remain as important sources of morbidity, if rarely of mortality.

The kidney is the master organ of homeostasis, guarding as it does the sanctity of the extracellular fluid, our "internal environment" (Claude Bernard). Renal microtitration of fluid, electrolytes, and metabolic constituents in the extracellular fluid comes at a cost. Urine composition must vary widely to accomplish this feat of homeostasis in the face of diverse dietary and metabolic challenges. The urine, né altered extracellular fluid, must then remain fluid and sterile in its long, slow passage between the ostia of the collecting tubules and the urethral meatus. Over the years, renal physiologists and internists have extensively studied the homeostatic role of the kidney, and urologists have become increasingly skilled in maintaining the patency of the

outflow pathway. Less attention, however, has been directed to what might be called the conduit chemistry of the urine itself.

In the study of kidney stones, a large number of approaches have been used. The epidemiology of stone diathesis is fascinating, albeit not very revelatory. "Stone belts" have been described in the United States and elsewhere without clear-cut demonstrable causes in soil, climate, or population ethnicity. Stone epidemics have also occurred, with both waxing and waning. For example, in the Norfolk and Norwich Hospital in England, 1 in every 38 patients admitted between 1772 and 1816 had a bladder stone.<sup>1</sup> Samuel Pepys, the diarist, exhibited his tennis ball-sized bladder stone annually at a special party at which the various calculi of the guests were admired. This type of stone has virtually disappeared in the West but has remained a problem in Southeast Asia.

It has also long been evident that stone diathesis may be familial. A number of genetic diseases may be primarily or exclusively manifested by the occurrence of kidney stones. Among these are cystinuria, primary hyperoxaluria (types 1 and 2), genetic forms of gout, the Lesch-Nyhan syndrome, xanthinuria, familial renal tubular acidosis, adenine phosphoribosyl-transferase deficiency (2,8-dihydroxyadenine stones), and probably many cases of idiopathic hypercalciuria. In some of these disorders, the explanation of stone pathogenesis is immediately apparent from a specific enzymatic abnormality. In others the link is not yet elucidated. Beyond these specific disorders, there are families with a stone diathesis, usually calcium oxalate in composition, for which no specific metabolic disorder has been defined.

In the study of stone pathogenesis, it is useful to consider two categories of variables: factors that result in increased concentrations in the urine of the crystalloid components of stones, and physicochemical changes in the urine (or urinary tract) conducive to stone formation at normal concentrations of crystalloids.<sup>2</sup> In the past, major attention has been largely directed to the first category because crystalloid concentration is the obvious driving force for the precipitation of stone constituents. The concentration of crystalloids in turn depends on two variables: the absolute amount of the substance excreted per unit of time and the volume of water in which that excretion occurs. Volume manipulation is a simple but important and often-neglected therapeutic maneuver in stone prophylaxis. Among the earliest investigations of a patient with a stone are determinations of whether there are increases in the excretion rates of these crystalloids, especially calcium, oxalate, cystine, uric acid, or ammonia (from urea-splitting organisms in infected urine).

The second category of stone pathogenesis—the variables other than crystalloid concentration—is less well understood. Urine pH may alter the effective concentration of a crystalloid (especially uric acid and magnesium ammonium phosphate). Stasis may allow time for the slow accretion of stone growth. It seems likely that many embryonic stones are harmlessly aborted through the urinary stream, as witnessed by crystal aggregates in a concentrated morning specimen. The possible pathogenetic role of abnormal stone matrix is still being investigated. The presence of a foreign body, most frequently another stone or even a few crystals, may serve as

a nidus of crystallization through the phenomenon of epitaxy. Perhaps of greatest importance, however, is the presence of protective substances in normal urine.

Do protective substances exist as natural water softeners in normal urine? Clearly they do. We daily excrete amounts of calcium, oxalate, and phosphate that cannot be dissolved in 1 to 2 liters of distilled water. In its wisdom the body has evolved mechanisms to maintain the metastability of these and other components in solution in the urine. Some of the participants in this protective system have long been known—citrate, magnesium, pyrophosphate, for example. Other components have been more newly discovered, or their potential roles more newly appreciated, such as the Tamm-Horsfall protein and nephrocalcin. The latter glycoprotein is particularly interesting because it is specifically synthesized in the renal tubule and contains the remarkable calcium-binding amino acid,  $\gamma$ -carboxyglutamic acid, the synthesis of which requires vitamin K. Patients with stone diathesis who do not exhibit excessive urinary concentrations of the offending crystalloids may well have abnormalities of these protective substances. It is intriguing to think that in the future it may be possible to increase urinary protective mechanisms and to decrease urinary crystalloid concentrations in the prophylaxis of stone growth or recurrence.

In this issue of the journal, Roger Sutton, DM, presents an interesting overview of the many aspects of stone pathogenesis, an area in which he has long had interest and to the understanding of which he has made many personal contributions.<sup>3</sup> The number of topics surveyed in this brief presentation reflects the extraordinary heterogeneity of this discipline—oxalate metabolism, calcium metabolism, urinary protective substances, primary hyperparathyroidism, idiopathic hypercalciuria, and some of the frontiers of research and of speculation in all of these areas. The subject matter is diverse because kidney stones themselves are diverse in composition and in pathogenesis. More than 50 years ago Howard Kelly wrote presciently, "No stretch of chemical or physical imagination will permit so heterogeneous a group of compounds (as renal stones) to be ascribed to a common origin, or their disposition in kidney, ureter, or bladder to be uniformly charged to an identical cause."<sup>4</sup> Pursuit of this heterogeneity enlivens all current research in this important medical problem.

Montaigne, who suffered much from kidney stones, wrote as follows: "I feel everywhere men tormented with same Disease; and am honour'd by the Fellowship, forasmuch as Men of the Best Quality are most frequently afflicted with it; 'tis a noble and dignified Disease. And were it not a good office to a man to put him in mind of his end? My kidneys claw me to purpose." Stones still too frequently claw our kidneys, but the new insights of conduit chemistry offer hope that this ancient malady can be both understood and arrested. Perhaps then we can truly and finally emerge from the Stone Age.

LLOYD H. SMITH, Jr, MD

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## Physicians and Animal Experimentation

ANIMAL EXPERIMENTATION has been vital in the development of the first polio vaccine, the isolation and use of insulin, the discovery of a vaccine for canine parvovirus (which causes a lethal infection in dogs), the production of antibiotics to treat pathologic microbes, research to improve cancer treatment, and the search for therapy against human immunodeficiency virus disease.<sup>1</sup> It is estimated that 17 to 22 million laboratory animals are used and killed each year, of which 90% are rodents and 1% to 2% are dogs and cats (150,000 to 200,000 animals).<sup>2</sup> To ensure appropriate and humane care of experimental animals, protective legislation was passed in the Animal Welfare Act of 1966 in the United States. In the 1970s and 1980s, a strong animal rights movement evolved in the United States intent on protecting animals and, in many cases, proposing that animals should have the same rights as human beings. For example, People for the Ethical Treatment of Animals state, "There is no rational basis for separating out the human animal. A rat is a pig is a dog is a boy. They're all animals."<sup>3</sup> Biomedical scientists and others are currently alarmed by the potential of the animal rights movement to convince the public to support and possibly pass restrictive legislation that would substantially decrease the ability of modern medical science to use animals in experiments.<sup>4</sup>

In this issue of the journal, Gelpi calmly and thoughtfully points out that there are two sides to the issue of animal experimentation and that physicians should educate themselves and become involved in this controversy.<sup>5</sup> Gelpi proposes that physicians as moderates "may be able to bring both sides of the animal rights controversy together in a spirit of mutual tolerance and in the common cause of promoting both human and animal welfare." This is a noble ideal and certainly worth the attention of physicians because extremism on either side is not acceptable.

Pardes and co-workers in their recent article on physicians and the animal rights movement underscored the extreme position of many of the animal rights organizations and called for clinicians to recognize the need for animal studies in the life sciences and to take responsibility for opposing what Woolsey called "the domination of knowledge by ignorance."<sup>4,6</sup> They pointed out that most health scientists are responsible and care for animals in a professional way. They called for vigilance in ensuring that scientists comply with regulations and that institutional review committees on animal research continue to do a careful job.

There is no question there have been examples of scientists and institutions who have not done a good job in caring for experimental animals in a humane way. In addition, it is questionable whether low-quality, duplicative, or mediocre research that results in the death of many animals should continue to be done.

The moral status of animals is at the basis of the disagreement between members of the animal rights movement and persons who support continued animal experimentation.<sup>7</sup> There is a moderate position that ascribes great moral worth to animals but allows them to be used for research under certain conditions.<sup>1</sup> This view is based on the principle of humane treatment, which obligates persons to use animals for research only when absolutely necessary and to minimize any suffering incurred by research. Investigators who believe they must use animals in their experiments should always ask